Nonspecific orofacial symptoms as risk factors for first-onset TMD and chronic TMD

Jenny Sun

Senior Honors Thesis
Department of Biostatistics
University of North Carolina at Chapel Hill
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Approved by:

Eric Bair

Dr. Eric Bair, Thesis Advisor

Jane Monaco

Dr. Jane Monaco, Reader

Dr. Gary Slade, Reader

ABSTRACT

Nonspecific orofacial symptoms as risk factors for first-onset TMD and chronic TMD
(Under the direction of Dr. Eric Bair)

Previous studies found the count of 6 nonspecific orofacial symptoms was one of the most important predictors of first-onset TMD. We further examined the influence of these symptoms (jaw siftness, cramping, fatigue, pressure, soreness, and ache) on first-onset TMD and chronic TMD among U.S. adults aged 18 to 44 years in the OPPERA study. We identified 259 first-onset TMD cases and 185 chronic TMD cases. Hazard ratios were computed to estimate the association between each nonspecific orofacial symptom and first-onset TMD. We calculated odds ratios to measure the association between each symptom and chronic TMD. A principal component analysis was used to determine if all six symptoms are measures of a single underlying construct or largely independent of one another. Multivariable cox models quantified the combined effects of non-specific orofacial symptoms, clinical orofacial measures, and first-onset TMD. Multivariable logistic models examined these same associations on chronic TMD. Each nonspecific orofacial symptom was significantly associated with increased incidence of first-onset TMD and greater odds of chronic TMD. Results from the principal component analysis suggest it is reasonable to summarize the six variables by simply counting the number of symptoms reported. In the multivariable analysis, nonspecific orofacial symptoms significantly predicted first-onset TMD (HR=1.33; 95% CI: 1.11-1.59) and chronic TMD (OR=3.06; 95% CI: 2.03-4.97). The results indicate that the count of nonspecific orofacial symptoms is an independent risk factor and not a surrogate variable for pain.

Introduction

Temporomandibular disorder (TMD) is an umbrella term used to describe musculoskeletal disorders in the temporomandibular region. This paper focuses on painful forms of TMD where the defining feature is pain in the temporomandibular joint or the masticatory muscles.[1, 2, 3] In the 2002 National Health Interview Survey, five percent of adults in the United States reported TMD-type pain (6% of women, 3% of men).[4] Longitudinal studies indicate that the average incidence rate is 4% of people per annum.[5] Most studies report that women have higher prevalence of painful TMD symptoms than men, with a female-to-male ratio of approximately 2:1. [6,7]

The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study was designed to identify potential risk factors for painful TMD. TMD etiology is multifactorial, with biological, psychological, and social models of causation currently favored. Although previous studies have identified risk factors for TMD, we could not clearly indicate whether risk factors predated TMD onset or were a consequence of TMD because of the cross-sectional study design. OPPERA overcomes this limitation by conducting a prospective cohort study of initially TMD-free individuals. By using this design, we can establish a temporal sequence that links risk factors measured prior to TMD onset to case development.[3]

Ohrbach and Bair previously explored clinical characteristics associated with TMD development.[8, 9] One characteristic evaluated was nonspecific orofacial symptoms, which are orofacial symptoms that are not primarily painful. These six symptoms were: jaw stiffness, cramping, fatigue, pressure, soreness, and ache. Bair found that count of 6 nonspecific orofacial symptoms was one of the most important predictors of first-onset

TMD. One hypothesis to explain this association is that nonspecific orofacial symptoms are merely a precursor to painful TMD, rather than an independent risk factor. If nonspecific orofacial symptoms are a surrogate variable for known risk factors, then the theoretical and practical relevance will be diminished.

The aim of this paper is to further investigate the influence of nonspecific orofacial symptoms on TMD onset and chronic TMD. Specifically, we will use principal components analysis to better understand the nature of this count of nonspecific orofacial symptoms. We also used multivariable regression to determine if the associations between this count and TMD can be explained by surrogate measures of clinical TMD or major risk factors for TMD (e.g., jaw pain or function limitation) or if it represents an independent risk factor for TMD.

Methods

Study Design

This paper reports findings from the OPERRA prospective cohort study of first-onset TMD and the baseline case-control study of chronic TMD. Study methods are explained briefly below and in more depth in previous papers.[10] The target population was community-based volunteers aged 18 to 44 years. To provide a demographically diverse sample, there were 4 recruitment sites: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL. Most participants heard of the study through advertisements, word of mouth, or email. The OPPERA project was reviewed and approved by institutional review boards at the 4 study sites and at the data-coordinating center, Battelle Memorial Institute. Study participants provided signed consent to participate. At

baseline, all participants completed a questionnaire, clinical examination, measurement of pain perception and autonomic function, and collection of a blood sample.

Trained examiners classified TMD based on the Research Diagnostic Criteria for Temporomandibular Disorders. Briefly, people were classified as chronic TMD cases if they met the following criteria: 1) frequently reported pain in the cheeks, jaw muscles, temples, or jaw joints during the past 6 months; 2) pain in the orofacial region for at least 5 days in the past month; and 3) evoked pain in at least 3 masticatory muscles or at least 1 tempormandibular joint in response to examiner's palpation of orofacial muscle palpation or jaw maneuver. The 6-month time criterion is consistent with the 1994 IASP recommended threshold for research in chronic pain.[13] First-onset TMD cases satisfied the following criteria: 1) pain within anatomic locations for more than 5 of the past 30 days and 2) examiner findings of pain in muscles, joints, or both from jaw maneuver and digital palpation of masticatory structures.[10] Participants classified as controls met the following criteria: 1) no previous diagnosis of TMD; 2) infrequent facial pain during the past 5 months and infrequent headache in the past 3 months; 3) no more than 4 days of facial pain in the past month; and 4) no use of night guard of occlusal splint.[12] Non-specific orofacial symptoms in the past month were assessed with a 6-item check list.

Study Design

The unmatched case-control study enrolled 3,247 controls and 185 chronic TMD cases between 2006 and 2008. Controls were selected among the participants in the prospective cohort study using a stratified random sample. Among the 3,247 controls, 2,731 completed at least one follow up questionnaire and were included in the

prospective cohort study. Follow-up questionnaires were conducted every 3 months through mid-2012 to screen for TMD symptoms. Questions inquired about "headaches or pain in your face, jaw, temples in front of the ear, or in the ear", which is defined as orofacial pain. The self-reported questionnaires were completed at home prior to a follow-up clinical examination. Examiners re-evaluated symptomatic study participants, and 259 people were classified with first-onset TMD. Examiners did not refer to questionnaire responses during the diagnosis of TMD. More detailed information about the follow-up questionnaires and clinical assessments can be found in other papers.[14]

Statistical Analysis

First, each non-specific orofacial symptom was individually assessed. The univariate association between each symptom and first-onset TMD was examined using Cox proportional hazards regressions. Hazard ratios (HRs), 95% confidence intervals (95% CIs), and p-values were computed. Although the hazard ratio is a theoretical construct, it provides a good approximate of the average incidence rate-ratio in a cohort study. The Cox proportional hazards models have convenient statistical advantages over other methods that model the incidence rate directly. HRs were adjusted for study site and the following demographics: age, gender (male, female) and race/ethnicity (White, African-American/Black, Hispanic, Asian, and Other). To evaluate the association between each non-specific orofacial symptom and chronic TMD, logistic regression was used. ORs, 95% CIs, and p-values were calculated. ORs were adjusted for study site and demographic variables.

Principal component analysis is a technique used to model the variation between a set of variables. This procedure was used to determine if all six symptoms are measures of a single underlying construct or if the variables are largely independent of one another. The correlation between each of the six symptoms was also computed.

Multivariable models were used to further examine the effects of nonspecific orofacial symptoms and determine whether non-specific orofacial symptoms act as a substitute variable for pain, jaw function limitation, or somatic awareness.A multivariable Cox regression model was used to estimate the combined effects of non-specific orofacial symptom count, various clinical pain measures, study site, and demographic variables on TMD incidence. The following clinical pain variables were included in the multivariable model: the Facial Pain Intensity Score from the Graded Chronic Pain Scale, the global score for the Pennebaker Inventory Limbic Languidness, and number of palpation tender points in the following regions: right temporalis, left temporalis, right masseter, left masseter, right mandibular, left mandibular, right lateral pterygoid, left lateral pterygoid, right temporomandibular (TM) joint, and left TM joint. Pain in response to palpation tender points in these regions is part of TMD case-classification. These clinical pain measures were selected because they may be a surrogate variable for the number of non-specific orofacial symptoms. Three separate models were tested: one crude model, one model adding demographics variables, and one model adding demographic and clinical pain variables. All models were adjusted for study site. HRs and 95% CIs were calculated. A multivariable logistic regression model was also conducted to examine the association between these same variables and chronic TMD. ORs and 95% CIs were computed from the same three types of models.

Results

Brief demographic information is reported in Table 1. More detailed descriptive statistics have been reported in previous OPPERA papers.[10] In the prospective cohort study, 2,731 initially TMD-free participants were followed for a total of 7,378 person-years (median=2.8 years/person). During this time, 259 people developed first-onset TMD. The baseline case-control study consisted of 185 chronic TMD cases and 3247 controls. Participants were more likely to be 18-24 years old (51.7%), female (58.6%), and white (51.6%).

Assessment of each non-specific orofacial symptom

Hazard ratios and 95% confidence intervals for the associations between each non-specific orofacial symptom and TMD incidence are presented in Table 2. For each non-specific orofacial symptom, presence of the symptom predicted TMD incidence. The strongest predictor of TMD incidence was cramping in the past 6 months (HR=3.09; 95% CI: 1.77-5.40). Cramping was reported in 4% of TMD cases. The weakest predictor is fatigue (HR=1.43; 95% CI: 0.90-2.25).

ORs and 95% CIs estimating the association between nonspecific orofacial symptoms and chronic TMD are displayed in Table 3. Each non-specific orofacial symptom is significantly associated with chronic TMD. Ache in the past 6 months is the strongest association (OR=167.36; 95% CI: 88.83-322.57). 95% of TMD cases reported jaw ache.

Relationship between the non-specific orofacial symptoms

Table 4 illustrates the correlation between each non-specific orofacial symptom. The 6 symptoms are moderately correlated, with correlations ranging from 0.40 to 0.63. Ache and soreness are the most correlated (r=0.63).

The scree plot for the principal component analysis is shown in Figure 1. The first component explains the majority of the variance (variances greater than 3.0). The five remaining components explain a smaller proportion of the variance in the data. All the loadings are approximately equal, indicating that it is reasonable to summarize the six variables by simply counting the number of symptoms reported.

Multivariable Models

The HRs and 95% CIs for the multivariable association between nonspecific orofacial symptoms and first-onset TMD are shown in Table 6. The count of nonspecific orofacial symptoms significantly predicts incidence of first-onset TMD in all 3 models. After adding clinical pain variables in model 3, the number of nonspecific orofacial symptoms remains significantly associated with increased incidence of first-onset TMD (HR=1.33; 95% CI: 1.11-1.59). This suggests that count of non-specific orofacial symptoms is not a substitute for any of the clinical pain variables, but rather an independent risk factor that is associated with increased incidence of first-onset TMD.

Table 7 displays the ORs and 95% CIs for the multivariable association between nonspecific orofacial symptoms and chronic TMD. In the first 2 models, the crude model and the model that includes demographic variables, the count of nonspecific orofacial symptoms is significantly associated with chronic TMD. When the clinical pain variables

were added in model 3, the symptom count was significantly associated with greater odds of chronic TMD (OR=3.06; 95% CI: 2.03-4.97).

Table 1. Descriptive Characteristics of OPPERA Study Participants

Characteristics; N (%)	Total	Baseline Case-Control Study: Cases (Chronic TMD)	Baseline Case-Control Study: Controls	Prospective Cohort Study: Cases (First On-Set TMD)	Prospective Cohort Study: Controls
All People	3432	185	3247	259	2472
Age (years)					
18-24	1773 (51.7)	72 (38.9)	1701 (52.4)	110 (42.5)	1307 (52.9)
25-34	919 (26.8)	60 (32.4)	859 (26.5)	78 (30.1)	656 (26.5)
35-44	740 (21.6)	53 (28.7)	687 (21.2)	71 (27.4)	509 (20.6)
Gender					
Male	1420 (41.4)	30 (16.2)	1390 (42.8)	92 (35.5)	1014 (41.0)
Female	2012 (58.6)	155 (83.8)	1857 (57.2)	167 (64.5)	1458 (59.0)
Race					
White	1771 (51.6)	128 (74.6)	1633 (50.3)	138 (53.3)	1304 (52.8)
Black	1030 (30.0)	25 (13.5)	1005 (31.0)	86 (33.2)	680 (27.5)
Asian	305 (8.9)	6 (3.2)	299 (9.2)	9 (3.5)	247 (10.0)
Hispanic	223 (6.5)	12 (6.5)	211 (6.5)	19 (7.3)	159 (6.4)
Other	103 (3.0)	4 (2.2)	99 (3.1)	7 (2.7)	82 (3.3)
Study Site					
Baltimore, MD	871 (25.4)	56 (30.3)	815 (25.1)	30 (11.6)	675 (27.3)
Buffalo, NY	820 (25.9)	23 (12.4)	797 (24.6)	71 (27.4)	622 (25.2)
Chapel Hill, NC	937 (27.3)	60 (32.4)	877 (27.0)	101 (39)	660 (26.7)
Gainesville, FL	804 (23.4)	46 (24.9)	758 (23.3)	57 (22.0)	515 (20.8)

Table 2. Univariate Associations between Non-Specific Orofacial Symptoms and Incidence Rate of First-Onset TMD

Symptom	TMD-free; N (%)	First-Onset TMD cases; N(%)	HR (95% CI)*	Adjusted HR (95% CI)**	P Value
Stiffness					
Yes	145 (6)	33 (13)	1.13 (0.74, 1.72)	1.80 (1.20, 2.71)	0.005
No	2323 (94)	225 (87)	1.00	1.00	
Cramping					
Yes	54 (2)	11 (4)	2.36 (1.23, 4.54)	3.09 (1.77, 5.40)	<0.001
No	2414 (98)	247 (96)	1.00	1.00	
Fatigue					
Yes	125 (5)	29 (11)	1.18 (0.78, 1.78)	1.43 (0.90, 2.25)	0.128
No	2342 (95)	229 (89)	1.00	1.00	
Pressure					
Yes	117 (5)	31 (12)	1.75 (1.20, 2.56)	1.80 (1.20, 2.71)	0.004
No	2350 (95)	227 (88)	1.00	1.00	
Soreness					
Yes	139 (6)	38 (15)	2.16 (1.51, 3.08)	2.20 (1.58, 3.06)	<0.001
No	2330 (94)	220 (85)	1.00	1.00	
Ache					
Yes	200 (8)	44 (17)	2.01 (1.46, 2.76)	2.12 (1.53, 2.93)	<0.001
No	2267 (92)	212 (83)	1.00	1.00	

*Adjusted for study site

**Adjusted for study site, age, gender, and race

Table 3. Univariate Associations Between Nonspecific Orofacial Symptoms and Chronic TMD

Symptom	TMD-free; N(%)	TMD cases; N(%)	OR (95% CI)*	Adjusted OR (95% CI)**	P Value
Stiffness					
Yes	215 (7)	169 (92)	163.66 (94.57, 283.22)	156.73 (90.00, 272.94)	<.001
No	3025 (93)	15 (8)	1.00	1.00	
Cramping					
Yes	83 (3)	79 (43)	30.96 (21.29, 45.03)	34.49 (22.95, 51.85)	<.001
No	3156 (97)	103 (57)	1.00	1.00	
Fatigue					
Yes	183 (6)	130 (71)	42.66 (29.84, 60.98)	42.08 (29.01, 61.03)	<.001
No	3054 (94)	52 (29)	1.00	1.00	
Pressure					
Yes	177 (5)	138 (75)	55.63 (38.24, 80.94)	48.51 (33.10, 71.09)	<.001
No	3060 (95)	46 (25)	1.00	1.00	
Soreness					
Yes	218 (7)	164 (90)	140.63 (84.04, 235.33)	135.32 (80.23, 228.24)	<.001
No	3022 (93)	18 (10)	1.00	1.00	
Ache					
Yes	300 (9)	173 (95)	183.34 (95.43, 352.25)	167.36 (86.83, 322.57)	<.001
No	2934 (91)	10 (5)	1.00	1.00	

*Adjusted for study site

**Adjusted for study site, age, gender, and race

Table 4. Correlation Matrix for Nonspecific Orofacial Symptoms

	Stiffness	Cramping	Fatigue	Pressure	Soreness	Ache
Stiffness	1.00	0.47	0.53	0.55	0.57	0.53
Cramping	0.47	1.00	0.41	0.43	0.42	0.40
Fatigue	0.53	0.41	1.00	0.47	0.47	0.44
Pressure	0.55	0.43	0.47	1.00	0.56	0.56
Soreness	0.57	0.42	0.47	0.56	1.00	0.63
Ache	0.53	0.40	0.44	0.56	0.63	1.00

Figure 1. Scree Plot of the Nonspecific Orofacial Symptoms PCA Results

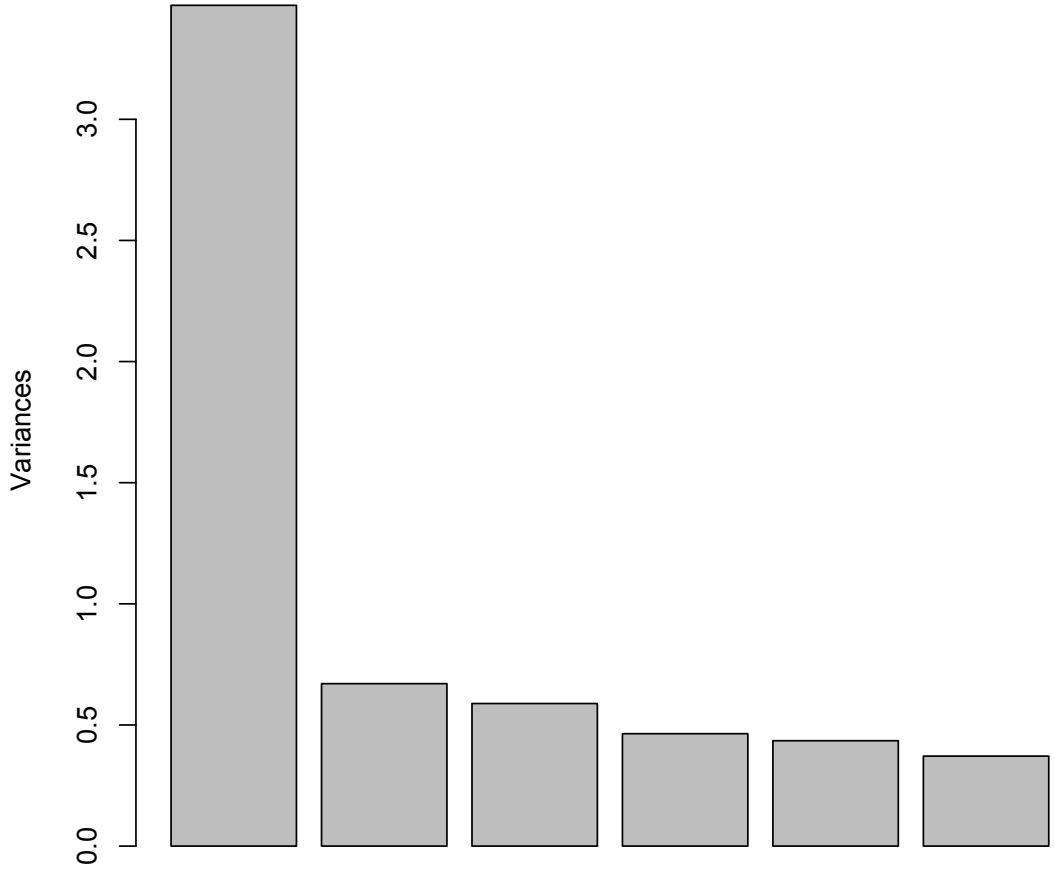

Table 5. Matrix of Loadings for the PCA Results of the First Component

	Stiffness	Cramping	Fatigue	Pressure	Soreness	Ache
PC1	-0.43	-0.36	-0.39	-0.42	-0.43	-0.42

Table 6. Multivariable-Adjusted Associations between Nonspecific Orofacial Symptoms and First-Onset TMD

		Model 1*		Model 2* Add: Demographics		Model 3* Add: Pain Measures	
Variable	**Coding**	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Number of nonspecific orofacial symptoms	z-score	1.32 (1.21, 1.45)	<0.001	1.31 (1.20, 1.43)	<0.001	1.23 (1.09, 1.39)	0.001

*All models adjusted for study site

Table 7. Multivariable-Adjusted Associations between Nonspecific Orofacial Symptoms and Chronic TMD

		Model 1*		Model 2* Add: Demographics		Model 3* Add: Pain Measures	
Variable	**Coding**	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**
Number of nonspecific orofacial symptoms	z-score	4.51 (3.80, 5.47)	<0.001	4.93 (4.03, 6.23)	<0.001	3.06 (2.03, 4.97)	<0.001

*All models adjusted for study site

Discussion

Bair previously found that count of 6 nonspecific orofacial symptoms was one of the most important predictor of first-onset TMD.[9] Here we show that during the median 2.8 follow-up years of the OPPERA prospective cohort study, each of the 6 nonspecific orofacial symptoms individually predicted incidence of TMD. In the baseline case-control study, each individual nonspecific orofacial symptom is also significantly associated with greater odds of chronic TMD. Though the correlation matrix shows that nonspecific orofacial symptoms are interrelated, the count of symptoms represents an individual construct. The principal component analysis further supports this conclusion, since the large majority of the variance was captured by the first component. Since each of the symptoms produced similar loadings, that indicates that a simple count of the symptoms provides an adequate measure of this construct.

In the multivariable analysis, the count of nonspecific orofacial symptoms is a significant predictor of first-onset TMD even after the addition of demographic variables and clinical pain measures. The significance of the symptom count in the fully adjusted model corroborates the hypothesis that count of nonspecific orofacial symptoms predicts chronic TMD independently of other risk factors. One hypothesis to explain the strength of the association between symptom count and TMD was that these symptoms represented measures of pain or preclinical TMD symptoms, so it would not be surprising that those with nonspecific orofacial symptoms converted to acute TMD. However, we now see that this is not the case, as the symptom count remains significant after including the pain variables. Indeed, the effect size of the symptom count is hardly modified when clinical pain measures are added. This suggests that the number of nonspecific orofacial

symptoms is not simply a surrogate variable for pain. These 6 symptoms were asked in the questionnaire to capture experiences that were seemingly adverse, but did not fit the definition of "pain" used for TMD case classification. Ohrbach previously suggested that the neurobiology underlying the semantics of the nonspecific orofacial symptoms is likely different from pain. These findings support Ohrbach's hypothesis.

In summary, the count of nonspecific orofacial symptoms represents an independent construct that predicts both first-onset and chronic TMD independently of other risk factors. The number of symptoms is not a substitute variable for pain, but its own its own risk factor.

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